Application of Zone Model Predictive Control Artificial Pancreas During Extended Use of Infusion Set and Sensor: A Randomized Crossover-Controlled Home-Use Trial

Gregory P. Forlenza,[1] Sunil Deshpande,[2,3] Trang T. Ly,[4] Daniel P. Howsmon,[5] Faye Cameron,[5] Nihat Baysal,[5] Eric Mauritzen,[6] Tatiana Marcal,[4] Lindsey Towers,[1] B. Wayne Bequette,[5] Lauren M. Huyett,[3,7] Jordan E. Pinsker,[3] Ravi Gondhalekar,[2,3] Francis J. Doyle III,[2,3] David M. Maahs,[1,4] Bruce A. Buckingham,[4] and Eyal Dassau[2,3]

Diabetes Care 2017;40:1096–1102 | https://doi.org/10.2337/dc17-0500

OBJECTIVE

As artificial pancreas (AP) becomes standard of care, consideration of extended use of insulin infusion sets (IIS) and continuous glucose monitors (CGMs) becomes vital. We conducted an outpatient randomized crossover study to test the safety and efficacy of a zone model predictive control (zone-MPC)–based AP system versus sensor augmented pump (SAP) therapy in which IIS and CGM failures were provoked via extended wear to 7 and 21 days, respectively.

RESEARCH DESIGN AND METHODS

A smartphone-based AP system was used by 19 adults (median age 23 years [IQR 10], mean 8.0 ± 1.7% HbA_{1c}) over 2 weeks and compared with SAP therapy for 2 weeks in a crossover, unblinded outpatient study with remote monitoring in both study arms.

RESULTS

AP improved percent time 70–140 mg/dL (48.1 vs. 39.2%; *P* = 0.016) and time 70–180 mg/dL (71.6 vs. 65.2%; *P* = 0.008) and decreased median glucose (141 vs. 153 mg/dL; *P* = 0.036) and glycemic variability (SD 52 vs. 55 mg/dL; *P* = 0.044) while decreasing percent time <70 mg/dL (1.3 vs. 2.7%; *P* = 0.001). AP also improved overnight control, as measured by mean glucose at 0600 h (140 vs. 158 mg/dL; *P* = 0.02). IIS failures (1.26 ± 1.44 vs. 0.78 ± 0.78 events; *P* = 0.13) and sensor failures (0.84 ± 0.6 vs. 1.1 ± 0.73 events; *P* = 0.25) were similar between AP and SAP arms. Higher percent time in closed loop was associated with better glycemic outcomes.

CONCLUSIONS

Zone-MPC significantly and safely improved glycemic control in a home-use environment despite prolonged CGM and IIS wear. This project represents the first home-use AP study attempting to provoke and detect component failure while successfully maintaining safety and effective glucose control.

[1]Barbara Davis Center, University of Colorado Denver, Denver, CO
[2]Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA
[3]William Sansum Diabetes Center, Santa Barbara, CA
[4]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA
[5]Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Troy, NY
[6]Department of Computer Science and Engineering, University of California San Diego, San Diego, CA
[7]Department of Chemical Engineering, University of California Santa Barbara, Santa Barbara, CA

Corresponding author: Eyal Dassau, dassau@seas.harvard.edu.

Received 10 March 2017 and accepted 6 May 2017.

Clinical trial reg. no. NCT02773875, clinicaltrials.gov.

G.P.F. and S.D. contributed equally to this study.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0500/-/DC1.

Improved glycemic control in type 1 diabetes via use of a closed-loop artificial pancreas (AP), which combines a continuous glucose monitor (CGM), continuous subcutaneous insulin infusion (CSII) pump, and insulin dosing control algorithm, has emerged as a priority in the past decade (1,2). Algorithms to control blood glucose (BG) using an AP include model predictive control (MPC), proportional integral derivative control, and fuzzy logic (3–8). Testing of AP systems has progressed from in silico models to hospital-based studies, followed by supervised hotel studies, and is now reaching prepivotal and pivotal outpatient testing (1,2,9,10). As AP systems evolve toward unsupervised home use, consideration of safety analysis and fault detection and mitigation becomes vital. Potential failure points in an AP system have been previously outlined and include insulin infusion sets (IIS), CGM sensors, CSII pump device, and communication failures (11). AP use during extended wear of IIS and CGMs provides a vital real-life test of glycemic control, as many subjects use their IIS and CGM longer than directed (12).

MPC has emerged as a popular control method for AP development, as it can be built around physiological understanding of diabetes, copes well with long dynamical effects and large time delays, can directly incorporate constraints on insulin delivery, and innately considers future projections of BG (4,13,14). MPC uses a mathematical model of glucose and insulin dynamics, real-time feedback from the CGM signal, and a cost function to optimize insulin infusion based on desired glucose outcomes (13,15). A zone-MPC algorithm attempts to maximize the time that BG spends in a specified target range where the controller adjusts insulin delivery only when BG is predicted to deviate from the target zone (13,16–18).

In this study, we tested a zone-MPC AP system (13,16–18) implemented on the University of Virginia Diabetes Assistant (DiAs) platform (19) using a Roche Accu-Chek Combo insulin pump and Dexcom G4 Platinum CGM in a remote-monitored home setting. Fault detection algorithms were in place to detect IIS and CGM sensor failure, and participants wore both the IIS and CGM sensor beyond the maximum recommended 3- and 7-day durations, respectively (20). Here we describe the success of glycemic control of the zone-MPC AP system versus sensor augmented pump (SAP) therapy in a randomized crossover comparison of system use at home, in a setting with increased chance of IIS and CGM sensor failures. We hypothesized that the AP arm would produce increased time in target range, decreased mean glucose, and decreased hypoglycemia compared with the SAP arm, despite conditions meant to increase the chance of system failure. This project represents the first home-use AP study testing system response to component failure through extended use while also testing the safety and efficacy of the AP system.

RESEARCH DESIGN AND METHODS

Study Design

Participants in this monitored outpatient study were recruited from two clinical centers (Barbara Davis Center [BDC] at the University of Colorado Denver and Stanford University). In total, 20 subjects were recruited and 19 completed the study, with 1 subject excluded due to failure to comply with study protocol (Supplementary Table 1 and Supplementary Fig. 1). Study applicants were included if they had a clinical diagnosis of type 1 diabetes, required daily insulin therapy for at least 12 months with a total daily dose (TDD) >0.3 units/kg/day, used a CSII pump for >3 months, used adequate pregnancy protection, were not pregnant, and had an adult cohabitant willing to tend to the subject during safety concerns. They were excluded if they had diabetic ketoacidosis or severe hypoglycemia in the past 6 months, used a long-acting insulin via injection or other antidiabetic medications within the past 8 weeks, used an oral/inhaled glucocorticoid, had a skin condition affecting sensor placement, or had other conditions that, in the opinion of the investigator, interfered with safe study participation. The primary outcome measures were related to fault detection, which will be briefly mentioned here with a full analysis in a future manuscript. For the zone-MPC AP performance, the outcome measures included mean sensor glucose value and percent of time in 70–180 mg/dL. Additional AP outcome measures were calculated based on the AP outcomes consensus paper (21). The study was approved by the FDA and the institutional review boards (IRBs) at the two clinical centers and is listed on clinicaltrials.gov (NCT02773875).

This outpatient study was conducted over 6 weeks (Supplementary Fig. 1), consisting of two 2-week blocks testing the use of a new infusion set for 7 days of prolonged wear, twice with either SAP or zone-MPC AP. Participants were permitted to use any type of steel or Teflon infusion set. A new CGM was inserted 1 week prior to each 2-week block to allow for a maximum of 3 weeks of sensor wear and to serve as a washout period between the first and second blocks. After enrollment, subjects were randomized in a 1:1 ratio to either group A or group B. Group A used the AP system with fault detection algorithms during the first block and group B used it during the second block. Subjects used SAP therapy with their personal CSII pump and a study-provided remotely monitored CGM.

During each block, subjects wore an IIS for up to 7 days or until IIS failure. IIS failure was defined as *1*) meter BG (MBG) >300 mg/dL with ketones of >0.6 mmol/L, *2*) failure of MBG to decrease by at least 50 mg/dL in response to a correction bolus, *3*) pump occlusion alarms, erythema, or induration >10 mm around the infusion site, or *4*) pain or discomfort. CGMs were placed at the start of the run-in week for each block and were worn for up to 3 weeks or until sensor failure. Sensor failure was defined as *1*) sensor failure notification on the receiver such as "Replace sensor," *2*) error message such as "???" for >2 h, *3*) inability to calibrate the sensor, *4*) persistent 20% difference between MBG and CGM value over 2 h with hourly readings, or *5*) failure to reconnect to the transmitter for 1 h.

During this outpatient trial, subjects used the AP at home and participated in their usual daily activities, including work, school, and athletics. Subjects made their own meal/food decisions without limitation or supervision and were instructed to bolus for meals as per their usual habits. Throughout the study, subjects were monitored remotely either through the DiAs web monitoring system (AP arm) or the Dexcom Share (SAP arm). During the AP arm, subjects were contacted for *1*) CGM value <60 mg/dL for >30 min, *2*) no CGM data with last CGM value <110 mg/dL, *3*) CGM value >300 mg/dL for >60 min, or *4*) CGM value >390 mg/dL. In addition, subjects were contacted for fault detection alerts for detected infusion set or CGM sensor failure. During the SAP arm,

subjects were contacted for CGM value <60 mg/dL for >30 min or for CGM value >300 mg/dL for >60 min.

Zone-MPC AP System

The AP algorithm deployed was the zone-MPC algorithm for insulin delivery along with the Health Monitoring System (HMS) for predictive hypoglycemia alarms (13,16,18). At each 5-min interval, the zone-MPC system uses explicit model predictions and online optimization of a cost to drive the subject's glucose to a predefined target zone. As long as the glucose predictions remain in the target zone, the system delivers the subject's predefined basal rates. If the BG is predicted to leave the target zone, then the algorithm automatically adjusts the insulin dose based on the current and historical CGM values, predicted trends, historical insulin delivery including insulin on board, and subject-specific information.

The system was initialized using the subject's TDD, insulin-to-carbohydrate ratio, correction factor, and basal rate profiles. Subjects were required to announce the meal carbohydrate content to the system. The standard meal bolus size was modified by zone-MPC based on the current MBG value (18). The amount of insulin not related to the meal bolus was optimized at each step, based solely on the CGM signal, subject parameters, and insulin infusion history, by solving an optimization problem that featured penalization of glycemic deviations with assertive corrections using glucose velocity (22) and an asymmetric cost on insulin to independently penalize hyperglycemic and hypoglycemic excursions (18). This insulin amount was subject to two safety constraints. First, the insulin dose was limited to be ≤1 unit except during the period of 2200 to 0400 h, when it was constrained to be <1.8 times the subject's basal rate. Second, the insulin amount was bounded by a constraint that uses the insulin on board and subject's correction factor to prevent insulin overdelivery (18,23).

Finally, the HMS ran in parallel to, and independently of, zone-MPC to provide an audio-visual advisory alarm when hypoglycemia was predicted to occur within the next 15 min (24). The study protocol required that subjects be contacted by study staff for a CGM glucose of <60 mg/dL for >30 min and that they take 16 g of fast-acting carbohydrates for a predicted hypoglycemia alarm and for an MBG of ≤80 mg/dL.

Statistical Analysis

Statistical analyses were performed on the basis of intention to treat; all data from each of the 19 participants were analyzed according to the arm of the study (AP or SAP). The calculations of glycemic metrics were based on the complete CGM data. Any missing data points due to sensor warmup and technical or connectivity issues were linearly interpolated. For each subject, the CGM time series was considered from 1800 h of the first day until 1200 h of the last day to exclude system startup and shutdown irregularities.

We calculated mean glucose using the complete CGM data over the study period. We also report median glucose to contrast it with mean glucose. To measure glucose variability, we used SD and coefficient of variation. We also report the fasting glucose using the CGM value closest to 0600 h. Data are presented either as mean ± SD or median (IQR). Statistical significance is calculated for paired data using signed-rank test and for independent samples using rank-sum test, where a 5% significance level is used to deem outcomes as significant. Within-subject difference in outcomes between the two study blocks were used to test for period effects (25). There were no corrections made for multiple comparisons.

We used linear regression, with robust fitting, to estimate a relationship between percent time in closed loop (percent CL, independent variable) and the change in within-subject glycemic performance from AP to SAP (*y*, dependent variable) as $y = \beta_0 + \beta_1$ (percent CL) + ε. The data analysis was performed using Matlab R2015b.

RESULTS

Subject Characteristics

This study consisted of 19 participants with a median age of 23.0 years (10.0), 11 female, with median type 1 diabetes duration of 11.0 years (11.8) (Supplementary Table 1). Baseline HbA_{1c} was 8.0 ± 1.7% (63.8 ± 18.4 mmol/mol), and TDD of insulin was 0.67 ± 0.19 units/kg/day.

Glycemic Control During Study Period

The glycemic metrics are summarized in Table 1. The zone-MPC AP system was superior to SAP therapy for the primary outcomes of increased percent time in the target range of 70–180 mg/dL (71.6 vs. 65.2%; *P* = 0.008) and decreased hypoglycemia (percent time <70 mg/dL, 1.3 vs. 2.7%; *P* = 0.001) (Fig. 1*B*). The AP system was superior for improvement in median glucose (141 vs. 153 mg/dL; *P* = 0.036) with clinically reduced mean glucose, which did not meet the statistical threshold of *P* < 0.05 (148 vs. 159 mg/dL; *P* = 0.059) (Fig. 1*A*). The AP system was also significantly superior to SAP therapy for the glycemic measures of increased percent time in the narrow target range 70–140 mg/dL (48.1 vs. 39.2%; *P* = 0.016), reduction in hypoglycemia percent time <50 mg/dL (0.1 vs. 0.2%; *P* = 0.007), and reduced percent time >180 mg/dL (24.9 vs. 30.9%; *P* = 0.030) and >300 mg/dL (0.4 vs. 1.8%; *P* = 0.025). The AP provided a significant reduction of glycemic variability as well (glucose SD 52 vs. 55 mg/dL; *P* = 0.044). The number of subjects below the recommended target of 7% HbA_{1c} (estimated mean glucose of 154 mg/dL) was 5 at enrollment based on measured HbA_{1c} and was 8 during SAP arm and 13 during AP arm based on estimated HbA_{1c}, out of a total of 19 subjects (26,27).

For the overnight period, the AP system was superior to SAP therapy for the primary end points of percent time 70–180 mg/dL (73.7 vs. 66.1%; *P* = 0.020) and reduction in hypoglycemia percent <70 mg/dL (0.7 vs. 1.5%; *P* = 0.004), but not for reduction in mean overnight glucose (151 vs. 159 mg/dL; *P* = 0.126) or median glucose (138 vs. 155 mg/dL; *P* = 0.064). However, the mean glucose at 0600 h was significantly lower in the AP arm (140 vs. 158 mg/dL; *P* = 0.020). Glycemic variability did not meet the threshold of statistical improvement for the overnight period (46 vs. 53 mg/dL; *P* = 0.053). No period-specific differences were found between the two sequences of the study (AP followed by SAP and vice versa) for any primary or secondary outcomes (Supplementary Table 3).

We also analyzed the day-by-day variation in 24-h mean glucose. In order to include the full 24-h data, we excluded the first and last day from this analysis. When compared on a day-by-day basis through the course of the study, the zone-MPC AP system reduced mean glucose compared with SAP on 11 out of 13 days (Fig. 2). Each mean data point (where the mean is taken across the subjects) is surrounded by a bubble corresponding to mean percent time

Table 1—Glycemic metrics comparing performance of zone-MPC AP arm with the SAP arm

	Day and night			Overnight		
Metric	SAP (n = 19)	AP (n = 19)	P value	SAP (n = 19)	AP (n = 19)	P value
% Time						
<50 mg/dL	0.2 (0.4)	0.1 (0.2)	0.007	0.0 (0.3)	0.0 (0.0)	0.067
<60 mg/dL	0.9 (1.2)	0.4 (0.4)	<0.001	0.6 (1.1)	0.0 (0.4)	0.020
<70 mg/dL	2.7 (2.3)	1.3 (1.2)	0.001	1.5 (1.7)	0.7 (1.3)	0.004
70–140 mg/dL	39.2 (13.3)	48.1 (10.5)	0.016	36.3 (16.2)	50.7 (19.0)	0.024
70–180 mg/dL	65.2 (10.4)	71.6 (9.8)	0.008	66.1 (16.5)	73.7 (13.4)	0.020
>180 mg/dL	30.9 (15.5)	24.9 (8.8)	0.030	32.7 (17.9)	25.4 (11.4)	0.030
>250 mg/dL	7.2 (3.5)	4.6 (4.8)	0.022	7.3 (7.0)	3.1 (4.6)	0.053
>300 mg/dL	1.8 (2.1)	0.4 (2.1)	0.025	1.0 (2.4)	0.0 (1.1)	0.277
Mean glucose (mg/dL)	159.0 (20.1)	148.3 (12.7)	0.059	159.4 (21.8)	150.9 (15.1)	0.126
Median glucose (mg/dL)	153.2 (22.7)	140.5 (14.9)	0.036	154.6 (30.0)	138.3 (24.7)	0.064
SD glucose (mg/dL)	55.1 (8.9)	51.9 (10.6)	0.044	53.2 (12.3)	46.4 (11.2)	0.053
Coefficient of variation glucose	0.4 (0.1)	0.3 (0.1)	0.099	0.3 (0.1)	0.3 (0.1)	0.198
Mean glucose at 0600 h (mg/dL)	158.3 (18.6)	139.6 (19.7)	0.020	—	—	—

The data are shown as median (IQR) under two columns: day and night and overnight (0000 to 0600 h). The significance is assessed by signed rank test. No period-specific differences were found between the two sequences of the study (Supplementary Table 3). Rows mean glucose and median glucose use the complete CGM signal over the study period. For the day and night column, 11 of 13 outcomes were significant, whereas for the overnight column, 5 of 12 outcomes were significant.

<70 mg/dL, where the AP systems reduced percent time <70 mg/dL for 12 out of 13 days. For day 8 in Fig. 2, the SAP mean was lower than zone-MPC mean by ~11 mg/dL; however, it came at the cost of a twofold increase in percent time in hypoglycemia.

Hypoglycemia During AP Arm

As stated above, the AP system was successful in decreasing overall and overnight hypoglycemia percent time <70 mg/dL. The AP hypoglycemic oral treatment burden was low during the study where the subjects required a mean of 0.85 ± 0.5 hypoglycemia treatments per day, consisting of a mean of 20 ± 8 g of carbohydrates per treatment. The amount of rescue carbohydrates consumed was not captured during the SAP arm. The median number of treatments required during the overnight period was 0.36 (1.17) per night, consisting of 17 ± 9 g of carbohydrates.

As both zone-MPC and HMS respond to impending hypoglycemia, by suspending insulin delivery and alarming the subject to treat with rescue carbs, respectively, we further analyzed the system performance in minimizing hypoglycemia exposure. We investigated events where the CGM value was <90 mg/dL for ≥20 min as potential hypoglycemia episodes. Of these potential episodes (average of 1.82 ± 0.46 events/day), subjects required an oral hypoglycemia treatment, on average, 44% of the time. There were no severe hypoglycemia events for which subjects required glucagon or the assistance of another person. There were no adverse events attributable to hypoglycemia.

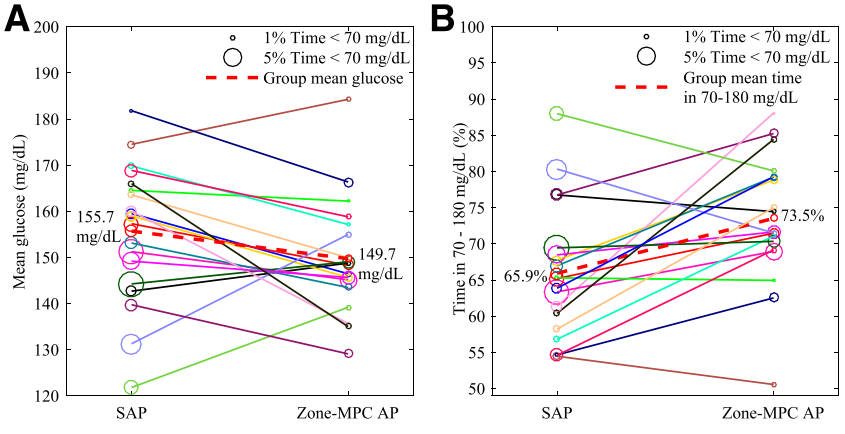

Figure 1—Paired comparison of mean glucose and time in target range (70–180 mg/dL) during SAP (control) and zone-MPC AP (experimental) arms. The solid lines connect individual subjects in this crossover study and display increase or decrease in the glycemic metric. The hypoglycemia exposure (time <70 mg/dL) is shown using a bubble with increased size signifying increased time in hypoglycemia during that arm. The dashed red line displays overall group results along with group mean as an annotation. The AP arm resulted in reduced mean BG (*A*) and improvement in time in range (*B*) for a majority of subjects (14 of 19). It also resulted in a decrease in time in hypoglycemia, as measured by time <70 mg/dL for the majority of subjects (18 of 19). Subjects are color coded with the same color between panels.

Glycemic Control and System Performance

The AP system operated under extended length of wear to induce infusion set and sensor failures, which could lead to disruption of closed-loop operation. We investigated whether the amount of time spent in closed loop had an effect on the relative improvement in glycemic control. Disruptions to closed loop were caused primarily by system disconnections (including sensor warmup period, loss of sensor signal, and communication irregularities), which occurred an average of 8 ± 3.2 times per day throughout the AP arm of the study. During the AP arm, subjects spent a mean of 91.7 ± 4% of their total time (mean 22 h/day) in closed loop. The percent time sensor values were 94.9 ± 2.5% in the AP arm and

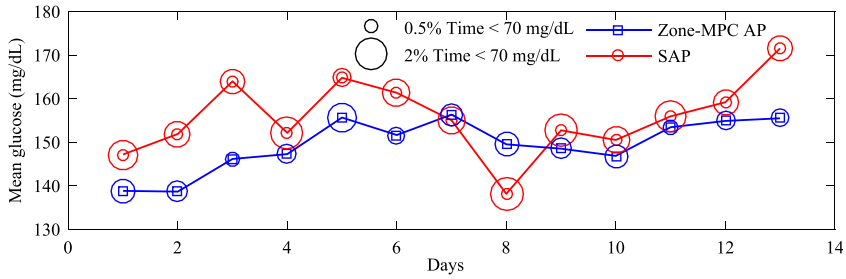

Figure 2—Plot of day-by-day mean glucose during SAP and zone-MPC AP arms. First and last day were excluded to include only days with a full 24 h of CGM data. The mean time <70 mg/dL is shown as varying size bubbles. The day-by-day mean glucose was lower during closed-loop use on 11 of 13 days.

93.8 ± 4% in the SAP arm (P = 0.54). The IIS fault detection algorithm had a sensitivity of 88% and was associated with a reduction in the median hyperglycemia time >250 mg/dL from 94 to 25 min (P < 0.001) in the 4 h before an IIS failure. The frequency of false alarms in closed loop with the IIS algorithm was 0.22 false alarms each day.

The estimated linear model between change in mean glucose from AP to SAP (y) and percent CL is shown in Fig. 3*A*. Through the model (R^2 = 0.38, β_1 = −1.92 [P = 0.006], 95% CI −3.23, −0.60), it is estimated that for each 1% increase in percent time in closed loop, the average decrease in mean glucose during the AP arm over the SAP arm is between 0.6 and 3.23 mg/dL. Figure 3*B* shows the same result when y is change in percent time in the 70–180 mg/dL range from AP to SAP. Through the model (R^2 = 0.32, β_1 = 1.49 [P = 0.012], 95% CI 0.35, 2.62), it is estimated that for each 1% increase in percent time in closed loop, the average increase in percent time in 70–180 mg/dL during the AP arm over the SAP arm is between 0.35 and 2.62%. Overall, the more time subjects spent in closed loop, the better improvements they saw in the outcomes. TDD during the AP arm was essentially the same as it was at enrollment (57 ± 20.8 vs. 56.3 ± 18.3 units/day; P = 0.21).

There was no difference in the number of infusion set failures (1.26 ± 1.44 vs. 0.78 ± 0.78 events; P = 0.13) and sensor failures (0.84 ± 0.6 vs. 1.1 ± 0.73 events; P = 0.25) between AP and SAP arms. Regression analysis comparing the number of IIS and CGM sensor failures against mean glucose and percent time in 70–180 mg/dL did not indicate that the number of failures was correlated with these outcomes (all P values >0.3). Comparison of subjects who experienced at least one infusion set failure against subjects who experienced no infusion set failures (in either arm) also failed to show significant differences between these groups for mean glucose (P = 0.32) or percent time in 70–180 mg/dL (P = 0.24).

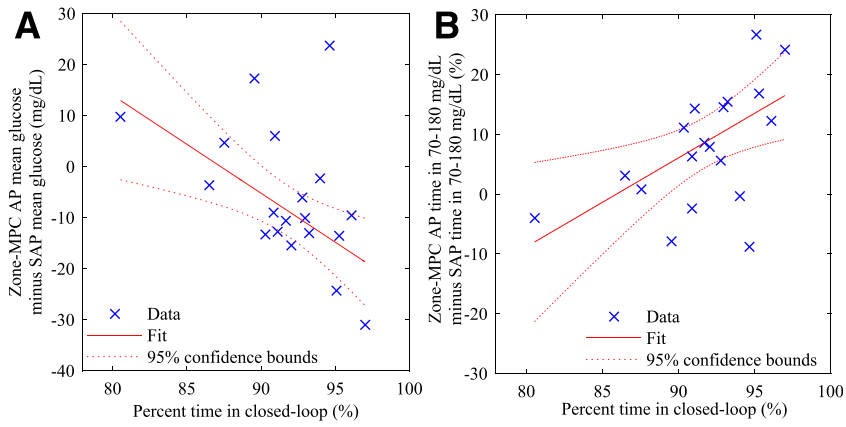

Figure 3—Analysis on relationship between glycemic changes, from zone-MPC AP to SAP, and the percent time the closed loop was active. The outcomes considered are change in mean glucose (R^2 = 0.38, β_1 = −1.92 [P = 0.006], 95% CI −3.23, −0.60) (*A*) and change in percent time in 70–180 mg/dL range (R^2 = 0.32, β_1 = 1.49 [P = 0.012], 95% CI 0.35, 2.62) (*B*). The time spent in closed loop correlates with improvement in glycemic outcomes.

Responders Versus Nonresponders

Analyzed individually, 14 of the 19 subjects showed a reduction in mean glucose during the AP arm over the SAP arm (responders), whereas 5 subjects showed an increase of mean glucose (nonresponders) (Fig. 1*A*). Fourteen of 19 subjects also showed improvement in percent time in 70–180 mg/dL (Fig. 1*B*). A majority of subjects (18 of 19) experienced a reduction in percent time <70 mg/dL. Among the subjects with an increase in mean glucose or decrease in time in range, four subjects were nonresponders for both mean glucose and time in range, one subject was a nonresponder for only mean glucose, and one subject was a nonresponder for only time in range. These six total subjects all had a significant reduction in hypoglycemia during the AP arm (Supplementary Table 2). Overall, the 6 nonresponders had a percent time in closed loop of 89.5 ± 5.1% and the 13 responders had a percent time in closed loop of 92.7 ± 2.8% (P = 0.17).

Estimating separate models for responders and nonresponders, between percent CL and the difference between percent time in the target range 70–180 mg/dL (Supplementary Fig. 2), revealed that for responders, the percent time in closed loop was strongly correlated with the amount of improvement in percent time in range (R^2 = 0.49, β_1 = 1.78 [P = 0.007], 95% CI 0.57, 2.99), whereas for nonresponders, the percent time in closed loop was completely unrelated to the amount of deterioration in percent time in range (R^2 = 0.02, β_1 = −0.12 [P = 0.78], 95% CI −1.28, 1.03).

CONCLUSIONS

This outpatient randomized crossover trial of the zone-MPC AP system demonstrates the safety and superiority of this AP system to SAP therapy. The AP system successfully reduced the median glucose value and increased percent time in the target range of 70–180 mg/dL while reducing hypoglycemia. The AP system also reduced glycemic variability and significantly improved mean glucose at 0600 h. Home use of this system did not result in any severe hypoglycemia or any severe adverse events.

Similar zone-MPC systems have been tested in the past in several clinical trials

(16,28–30). Huyett et al. (28) investigated zone-MPC as a hybrid AP system in 10 adolescents during a 72-h supervised hotel stay. In that study, the mean glucose value (150 ± 19 mg/dL) and percent time in target range 70–180 mg/dL (71 ± 10%) were very similar to the results from this trial, whereas the percent time <70 mg/dL (2.5 ± 1.8%) was slightly higher than for this trial. Dassau et al. (30) investigated 32 subjects undergoing two 27-h zone-MPC AP sessions, with either unchanged or algorithmically adjusted tuning of AP parameters. They found mean glucose for both control and tuned parameters (142 and 141 mg/dL), percent time <70 mg/dL (1.34 and 1.37%), and percent time in target range 70–180 mg/dL (79 and 75%), which were comparable to the results from our study.

The first commercially available hybrid closed-loop system, the Medtronic 670G, was approved in 2016 for sale in 2017, for which the results of the pivotal clinical trial have recently been published (31,32). That study investigated 3-month at-home use of an AP system without remote monitoring. For the adult cohort, the mean glucose value (148.3 ± 13.5 mg/dL) and percent time in target range 70–180 mg/dL (73.8 ± 8.4%) were almost identical to the control during AP use in our trial, and the percent time <70 mg/dL (3.4 ± 2.1%) was somewhat higher than seen during our trial. The adult group was in Auto Mode (in closed loop) for a median of 21.1 h/day (88% of the time), which was somewhat less than for our study, although the Medtronic study ran for a longer duration and percent usage often decreases with study duration. The zone-MPC system compared favorably with the recently commercially approved 670G system in adult outpatient use despite the prolonged CGM and IIS wear.

Of particular interest in the analysis of the subjects from this study were the six nonresponders. The five subjects for whom AP led to an increase in mean glucose showed an average increase of 12 ± 8 mg/dL while showing a decrease in percent time <70 mg/dL of 2.7 ± 1.5%, an improvement twice that seen for the overall cohort (1.4% improvement overall). The five subjects for whom AP led to a decrease in percent time in the target range 70–180 mg/dL showed an average decrease of 4.7 ± 3.6% time in target while showing a decrease in percent time <70 mg/dL of 2.0 ± 1.6%. For responders, closed-loop use is highly correlated with amount of improvement in target range, whereas for nonresponders, there was essentially no correlation between percent time in range and percent time in closed loop. Nonresponders had high levels of hypoglycemia at baseline and their overall control could have improved via less low BG while their average and time in target range may not have changed, or even worsened. As the zone-MPC system uses the subject's preset basal rates in addition to carbohydrate ratios, the AP system may have been sensitive to poorly tuned pump settings for these individuals, causing the percent time in closed loop to not improve overall control.

This study also tested the ability of an automated fault detection algorithm to detect impending IIS and CGM sensor failures. Several previous studies investigating the impact of prolonged IIS wear have shown that whereas the risk of IIS failure rises with the length of time a unit is worn, the mean glucose and TDD do not change between day 1 and day 7 of IIS wear (33,34). Similar results were seen in this study whereby the day of the study did not appear to impact the mean glucose or the percent time in hypoglycemia (Fig. 2).

This study has several notable strengths. It was an outpatient, randomized, crossover multicenter trial, which increases the generalizability when compared with earlier AP studies. The control condition consisted of subjects using SAP therapy with remote monitoring, which is a very high level of therapy against which to compare an AP system. That the participants were wearing a CGM and IIS for a prolonged period of time further strains the system and allows for a less than optimal set of conditions, further improving generalizability. A weakness of this study was the 24-h physician remote monitoring of the participants using the AP system, which improved participant safety but limits generalizability.

In conclusion, the zone-MPC AP system was successful in improving glycemic control while also reducing hypoglycemia in an outpatient setting designed to precipitate IIS and CGM sensor failure. This system was safe and functioned without adverse events in a home-use environment. Future work will focus on further refinement of the system and progression to sparsely supervised outpatient trials of larger size and longer duration.

Acknowledgments. The authors first thank the patients who participated in the clinical trial, as well as their families and support teams, who made this work possible. Research device support was provided by Roche AG (Basel, Switzerland) and Dexcom, Inc. (San Diego, CA). The authors thank the University of Virginia Center for Diabetes Technology for their support with the use of the DiAs AP platform. The authors acknowledge work by the diabetes technology teams at Stanford University and the BDC, who contributed many overnight and weekend hours to this project. Study data were collected and managed using REDCap electronic data capture tools hosted at Stanford University. The authors thank the following members of the zone-MPC/fault detection group for their support in facilitating this clinical trial: Dr. Paul Wadwa, Dr. Robert Slover, Laurel Messer, Emily Jost, Emily Westfall, and Cari Berget (BDC); Paula Clinton (Stanford University); and Elaine Schertz (University of Virginia).

Funding. This work was funded by a grant from JDRF (17-2013-471). The Clinical Translational Research Unit at Stanford University was funded by National Institutes of Health grant UL1-TR-001085. The development of the zone-MPC system was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DP3-DK-094331 and DP3-DK-104057).

Duality of Interest. G.P.F. is a consultant for Abbott Diabetes Care and receives grant funding from Medtronic, Dexcom, Animas, Tandem, Bigfoot Biomedical, and Insulet. T.T.L. has received research funding from Medtronic and Tandem and is currently employed by Insulet. B.W.B. has served as a consultant for Becton, Dickinson and Company. R.G. receives royalty payments on intellectual property related to the MPC algorithm used in this study. F.J.D. and E.D. have patents on the underlying MPC algorithms used in the study and are currently receiving royalty payments on these patents. D.M.M. is on the advisory board for Insulet; is a consultant for Abbott Diabetes Care; and receives research funding from Medtronic, Roche, and Dexcom. B.A.B. has received research support from Medtronic, Dexcom, Insulet, Roche, Tandem, and Bigfoot Biomedical; is on advisory boards for Sanofi, Novo Nordisk, and Becton, Dickinson and Company; and was a consultant for Dexcom. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.P.F. wrote the introduction, methods, results, and discussion and conducted the clinical trial at the BDC. S.D. conducted the data analysis, cowrote the methods and results, and provided engineering support during the trial. T.T.L. wrote the protocol, conducted the clinical trial at Stanford University, and reviewed the manuscript. D.P.H. reviewed the manuscript, assisted with data analysis, designed the fault detection algorithm, and provided engineering support throughout the trial. F.C. reviewed the manuscript and contributed to the fault detection algorithm. N.B. reviewed the manuscript and contributed to the fault detection design. E.M. developed the remote monitoring system used in the fault detection portion of the study. T.M. assisted

with development of the protocol, coordinated IRB submission and study procedures at Stanford University, and reviewed the manuscript. L.T. coordinated IRB submission and study procedures at BDC and reviewed the manuscript. B.W.B. reviewed the manuscript, oversaw development of the fault detection algorithm, and provided engineering support during benchtop testing. L.M.H. contributed to the protocol, study planning and preparations, and system testing and reviewed the manuscript. J.E.P. assisted with protocol development, U.S. Food and Drug Administration Investigational Device Exemption submission, and engineering support and reviewed the manuscript. R.G. developed the zone-MPC system, provided engineering support during the trial, and reviewed the manuscript. F.J.D. contributed to the design of the grant and the protocol, developed the zone-MPC system, and reviewed the manuscript. D.M.M. contributed to the design of the grant and the protocol, assisted with writing the manuscript, reviewed the manuscript, and conducted the protocol at the BDC. B.A.B. wrote the protocol, conducted the clinical trial at Stanford University, reviewed the manuscript, and was the overall principal investigator on this grant. E.D. contributed to the design of the grant and protocol, developed the zone-MPC system, assisted with writing the manuscript, and reviewed the manuscript. E.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Preliminary analysis of this study was presented at the 10th International Conference on Advanced Technologies & Treatments for Diabetes, Paris, France, 15–18 February 2017.

References

1. Forlenza GP, Buckingham B, Maahs DM. Progress in diabetes technology: developments in insulin pumps, continuous glucose monitors, and progress towards the artificial pancreas. J Pediatr 2016;169:13–20
2. Kowalski A. Pathway to artificial pancreas systems revisited: moving downstream. Diabetes Care 2015;38:1036–1043
3. Doyle FJ 3rd, Huyett LM, Lee JB, Zisser HC, Dassau E. Closed-loop artificial pancreas systems: engineering the algorithms. Diabetes Care 2014; 37:1191–1197
4. Bequette BW. Algorithms for a closed-loop artificial pancreas: the case for model predictive control. J Diabetes Sci Technol 2013;7:1632–1643
5. Pinsker JE, Lee JB, Dassau E, et al. Randomized crossover comparison of personalized MPC and PID control algorithms for the artificial pancreas. Diabetes Care 2016;39:1135–1142
6. Steil GM. Algorithms for a closed-loop artificial pancreas: the case for proportional-integral-derivative control. J Diabetes Sci Technol 2013;7: 1621–1631
7. Ruiz JL, Sherr JL, Cengiz E, et al. Effect of insulin feedback on closed-loop glucose control: a crossover study. J Diabetes Sci Technol 2012;6:1123–1130
8. Mauseth R, Hirsch IB, Bollyky J, et al. Use of a "fuzzy logic" controller in a closed-loop artificial pancreas. Diabetes Technol Ther 2013;15:628–633
9. Kropff J, DeVries JH. Continuous glucose monitoring, future products, and update on worldwide artificial pancreas projects. Diabetes Technol Ther 2016;18(Suppl. 2):S253–S263
10. Thabit H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia 2016;59:1795–1805
11. Bequette BW. Fault detection and safety in closed-loop artificial pancreas systems. J Diabetes Sci Technol 2014;8:1204–1214
12. Heinemann L, Krinelke L. Insulin infusion set: the Achilles heel of continuous subcutaneous insulin infusion. J Diabetes Sci Technol 2012;6:954–964
13. Grosman B, Dassau E, Zisser HC, Jovanovič L, Doyle FJ 3rd. Zone model predictive control: a strategy to minimize hyper- and hypoglycemic events. J Diabetes Sci Technol 2010;4:961–975
14. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743–751
15. Parker RS, Doyle FJ 3rd, Peppas NA. A model-based algorithm for blood glucose control in type I diabetic patients. IEEE Trans Biomed Eng 1999;46: 148–157
16. Harvey RA, Dassau E, Bevier WC, et al. Clinical evaluation of an automated artificial pancreas using zone-model predictive control and health monitoring system. Diabetes Technol Ther 2014; 16:348–357
17. Kovatchev B, Patek S, Dassau E, et al.; Juvenile Diabetes Research Foundation Artificial Pancreas Consortium. Control to range for diabetes: functionality and modular architecture. J Diabetes Sci Technol 2009;3:1058–1065
18. Gondhalekar R, Dassau E, Doyle FJ 3rd. Periodic zone-MPC with asymmetric costs for outpatient-ready safety of an artificial pancreas to treat type 1 diabetes. Automatica (Oxf) 2016;71:237–246
19. Keith-Hynes P, Guerlain S, Mize B, et al. DiAs user interface: a patient-centric interface for mobile artificial pancreas systems. J Diabetes Sci Technol 2013;7:1416–1426
20. Howsmon DP, Cameron F, Baysal N, et al. Continuous glucose monitoring enables the detection of losses in infusion set actuation (LISAs). Sensors (Basel) 2017;17:pii: E161
21. Maahs DM, Buckingham BA, Castle JR, et al. Outcome measures for artificial pancreas clinical trials: a consensus report. Diabetes Care 2016;39: 1175–1179
22. Gondhalekar R, Dassau E, Doyle FJ III. Velocity-weighting to prevent controller-induced hypoglycemia in MPC of an artificial pancreas to treat T1DM. Proc Am Control Conf 2015;2015:1635–1640
23. Ellingsen C, Dassau E, Zisser H, et al. Safety constraints in an artificial pancreatic beta cell: an implementation of model predictive control with insulin on board. J Diabetes Sci Technol 2009;3:536–544
24. Harvey RA, Dassau E, Zisser H, Seborg DE, Jovanovič L, Doyle FJ III. Design of the health monitoring system for the artificial pancreas: low glucose prediction module. J Diabetes Sci Technol 2012;6:1345–1354
25. Hills M, Armitage P. The two-period crossover clinical trial. Br J Clin Pharmacol 1979;8:7–20
26. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478
27. American Diabetes Association. Glycemic targets. Sec. 5. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1): S39–S46
28. Huyett LM, Ly TT, Forlenza GP, et al. Outpatient closed-loop control with unannounced moderate exercise in adolescents using zone model predictive control. Diabetes Technol Ther. 1 May 2017 [Epub ahead of print]. DOI: 10.1089/dia.2016.0399
29. Zisser H, Dassau E, Lee JJ, Harvey RA, Bevier W, Doyle FJ 3rd. Clinical results of an automated artificial pancreas using technosphere inhaled insulin to mimic first-phase insulin secretion. J Diabetes Sci Technol 2015;9:564–572
30. Dassau E, Brown SA, Basu A, et al. Adjustment of open-loop settings to improve closed-loop results in type 1 diabetes: a multicenter randomized trial. J Clin Endocrinol Metab 2015;100:3878–3886
31. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016; 316:1407–1408
32. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155–163
33. Patel PJ, Benasi K, Ferrari G, et al. Randomized trial of infusion set function: steel versus teflon. Diabetes Technol Ther 2014;16:15–19
34. Karlin AW, Ly TT, Pyle L, et al. Duration of infusion set survival in lipohypertrophy versus nonlipohypertrophied tissue in patients with type 1 diabetes. Diabetes Technol Ther 2016;18: 429–435